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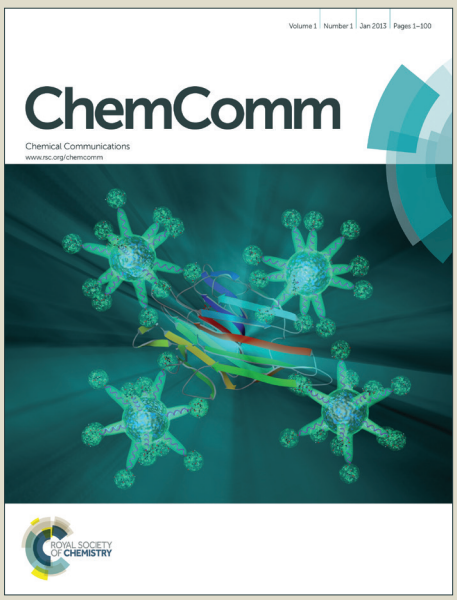

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ARTICLE TYPE

Palladium(0)-catalyzed cyclopropanation of benzyl bromides *via* C(sp^3)-H bond activation

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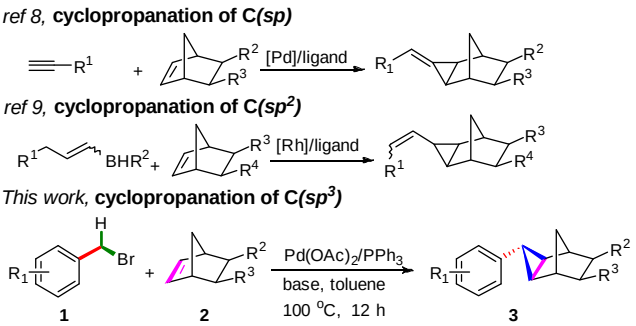
A novel and highly efficient Pd(0)-catalyzed domino reaction to prepare cyclopropane derivatives has been established. The process involves a Heck-type coupling and a C(sp^3)–H bond activation. Preliminary DFT calculations suggest that a four-membered palladacycle intermediate is involved.

Due to the smallest bonding angle and corresponding unique properties, synthesis and transformations of cyclopropanes have attracted tremendous interest of chemists.[1] The cyclopropane subunit is also found in many natural products and unnatural pharmaceuticals, so studies on their synthetic stratagies were further propelled.[2] A general method for the synthesis of cyclopropane derivative is the addition of carbenes to alkenes.[3] The Simmons–Smith reaction is also an important method for converting carbon-carbon double bonds to cyclopropane rings.[4] Michael-initiated ring closure (MIRC)[5] and intramolecular cycloisomerization of designed highly-unsaturated molecules[6] are delicate strategies to install a cyclopropane unit. Transition metal catalyzed transformations may become the most efficient and powerful methodology to construct structurally diverse small ring compounds. A few examples for making cyclopropanes *via* C−H or C–C bond activation have been reported.[7,8,9,10]



Scheme 1. Strategies for the formation of cyclopropanes.

Buono and co-workers reported Pd-catalyzed cyclopropanation of terminal alkynes with norbornene derivatives *via* C(*sp*)−H bond activation (Scheme 1).[8] Lautens and Murakami reported rhodium-catalyzed tandem vinylcyclopropanation of vinylboronic compounds to strained alkenes.[9] However, cyclopropanation *via* C(sp^3)−H bond activation remains underdeveloped, with only one example of Rh(1)-catalyzed intramolecular cyclopropanation reported by Sato.[10] Intermolecular cyclopropanation of simple molecules *via* C(sp^3)−H bond activation has not been reported. Herein, we report the first example of intermolecular C(sp^3)−H activation cyclopropanation catalyzed by Pd(0) (Scheme 1).

Norbornene[11] and Cyclopropane-fused norbornene skeleton[12] present in many natural products and pharmaceuticals and exhibit biological activity. Cyclopropane-fused dicyclopentadienes are also used as high energetic materials.[13] Cyclopropane-fused norbornene and dicyclopentadiene were useful precursors of cycloisomerization in organic synthesis.[14]

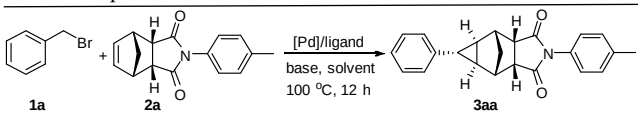
Based on our interesting in the cyclopropane-fused norbornene derivatives and envisioning for Pd(0)-catalyzed cyclopropanation of norbornenes *via* C(sp^3)−H bond activation,[15] benzyl bromide **1a** and *endo*-*N*-(*p*-tolyl) norbornenesuccinimide **2a** were employed as model substrates to perform the reaction. The desired product **3aa** was obtained when the reaction was catalyzed by $Pd(OAc)_2/PPh_3$. So the reaction parameters were investigated and the results are summarized in table 1.

Firstly, the metal catalyst and the ligand were screened in the [2+1] cycloadditions. $Pd(OAc)_2$ was better than $PdCl_2$ and $Pd(PPh_3)_4$ (Table 1, entries 4, 9 and 10, 91% yield compared with 64% and 72%). $Pd(dppf)Cl_2$ did not give the desired product, possibly because of steric effect from the sterically encumbered ligand. The effect of the ligand was also important. In contrast to PPh_3 (entry 4, 91% yield), BINAP was not effective in this reaction, and TMOPP resulted in a lower yield of **3aa** (entry 13, 53%). The base also had a significant effect on the yield of the reaction product. *t*-BuOK, Cs_2CO_3, and K_3PO_4 gave the low to good yield respectively (Table 1, entries 1, 2 and 6, 31%-76%). $NaNH_2$ and DBU were not effective. The use of KOH as a base provided a complex mixture. Compared to K_2CO_3, CH_3ONa was the best in promoting this reaction (Table 1, entries 3 and 4). The effects of solvent and temperature were also investigated. The reaction could be conducted successfully in toluene (Table 1, entry 4). Other polar aprotic solvents, such as CH_3NO_2 and dioxane only gave low or moderate yields (Table 1, entries 14 and 15), while DMF resulted in a failure reaction (Table 1, entry 16). Reduced reactivity and conversion were observed when the reaction was performed at 90 °C (entry 17, 51%). For the model reaction, the best yield was obtained when the reaction was catalyzed by $Pd(OAc)_2/PPh_3$ and CH_3ONa was employed as base in toluene (Table 1, entry 4, 91%).

With the optimized reaction conditions in hand, the substrate scope was examined using varieties of benzyl bromides **1** and norbornene derivatives **2**, as shown in Table 2. In general, benzyl

bromides bearing electron-donating groups provided corresponding cyclopropane products in higher yields than those containing electron-withdrawing groups (except for **3da**). The benzyl bromides substituted by methyl or methoxy group afforded product **3** in good to excellent yields (Table 2, **3ba-3da, 3bb, 3bc-3cc, 3ic, 3bd-3cd, 3id**). Benzyl bromides bearing electron-withdrawing groups (fluoro and chloro) also provided products **3** in good to high yields (Table 2, **3ea-3ha, 3eb-3gb, 3gc, 3ed-3gd**). The *ortho*-methyl and chloro benzyl bromides could not give pure products because of their steric hindrance. The structure of **3aa** is further unambiguously elucidated by X-ray crystallography (see the SI, Figure 1). On the basis of the chemical shifts and coupling constants (*J*) of all the products as well as the NOESY analysis of **3aa, 3ea** and **3ic**, it can be ascertained that the stereochemistry of all the compounds is the same with that of **3aa**. In addition, they are all the sole diastereomers obtained in each case.

Table 1. Optimization of reaction conditions [a]



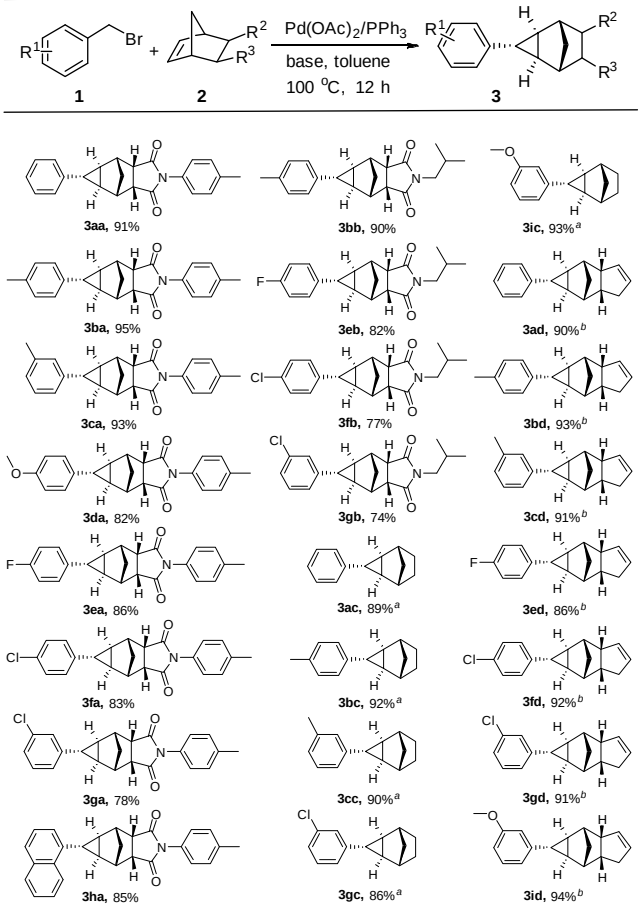
entry	[Pd]	ligand	base	solvent	yield(%)
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	54
2	$Pd(OAc)_2$	PPh_3	K_3PO_4	toluene	76
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	80
4	$Pd(OAc)_2$	PPh_3	CH_3ONa	toluene	91
5	$Pd(OAc)_2$	PPh_3	$NaNH_2$	toluene	NR[b]
6	$Pd(OAc)_2$	PPh_3	t-BuOK	toluene	31
7	$Pd(OAc)_2$	PPh_3	DBU	toluene	NR[b]
8	$Pd(OAc)_2$	PPh_3	KOH	toluene	-[c]
9	$PdCl_2$	PPh_3	CH_3ONa	toluene	64
10	$Pd(PPh_3)_4$	PPh_3	CH_3ONa	toluene	72
11	$Pd(dppf)Cl_2$	PPh_3	CH_3ONa	toluene	-[c]
12	-	-	CH_3ONa	toluene	NR[b]
12	$Pd(OAc)_2$	BINAP	CH_3ONa	toluene	NR[b]
13	$Pd(OAc)_2$	TMOPP[d]	CH_3ONa	toluene	53
14	$Pd(OAc)_2$	PPh_3	CH_3ONa	CH_3NO_2	34
15	$Pd(OAc)_2$	PPh_3	CH_3ONa	Dioxane	56
16	$Pd(OAc)_2$	PPh_3	CH_3ONa	DMF	NR[b]
17	$Pd(OAc)_2$	PPh_3	CH_3ONa	toluene	51[e]

[a] Reaction conditions unless otherwise noted: **1a** (0.55 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), ligand (0.11 mmol), base (1.5 mmol), solvent (2.0 mL), 100 °C, 12 h in sealed tube. Isolated yields. [b] No reaction. [c] No product. [d] TMOPP=tris(4-methoxylphenyl)phosphine. [f] 90°C.

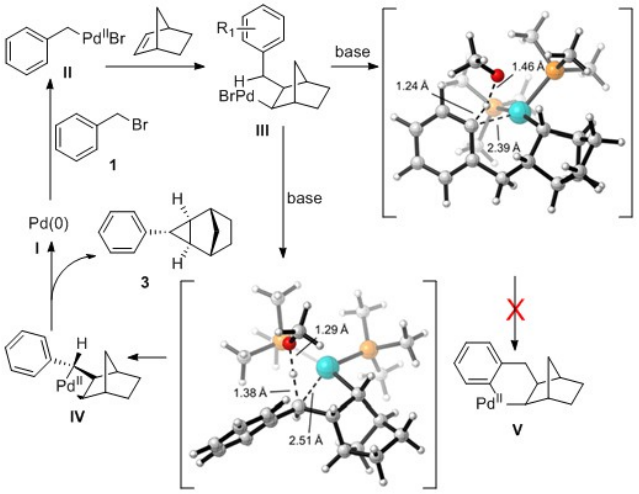
Substituted norbornene substrates were also examined. Norbornene itself afforded the expected corresponding benzylcyclopropane products (Table 2, **3ac-3cc**, **3gc**, **3ic**) in good to excellent yields (90%-93%) in the presence of 0.5 equiv K_2CO_3 and 3.0mL toluene at 120°C. Functionalized norbornenes afforded the corresponding products in good to excellent yields (Table 2, **3aa-3ha**, **3bb**, **3fb-3gb**, 77%-96%) in the presence of 1.5 equiv CH_3ONa and 2.0mL toluene at 100°C. Dicyclopentadiene afforded the desired products (Table 2, **3ad-3gd**, **3id**) with good to excellent yields in the presence of 0.5 equiv K_2CO_3 and 3.0 mL toluene at 100°C.

In order to better understand the reaction mechanism, the blank test without $Pd(OAc)_2/PPh_3$ was performed (Table 1, entry 12) and no reaction occurred. So the reaction should not proceed through carbene intermediate. Benzyl bromide could not eliminate to carbene under this reaction condition.

Table 2. Substrate scope of Pd(0)-catalyzed cyclopropanation.



Reaction conditions unless otherwise noted: **1** (0.55 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.11 mmol), CH_3ONa (1.5 mmol), toluene (2.0 mL), 100 °C, 12 h in sealed tube. Isolated yields. [a] **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (0.25 mmol), toluene (3.0 mL), 120 °C, 12 h. [b] **1** (0.5 mmol), 2 (0.5 mmol), K_2CO_3 (0.25 mmol), toluene (3.0 mL), 100 °C, 12 h.



Scheme 2. Plausible reaction mechanism and DFT calculations on deprotonation process for **TS1a** and **TS1b**.

Based on the above results and earlier precedents,[10,16] a putative mechanism was proposed (Scheme 2). The oxidative

addition of palladium(0) species to benzyl bromides generated a benzylpalladium(II) species **II**. Subsequent Heck-type carbopalladation at the *exo*-face of the norbornene gave norbornenylpalladium complex **III**, which undergowent C(sp^3)-H bond activation on the methylene of benzyl and generated a palladacycle **IV**. DFT calculations on the deprotonation process showed that the **TS1a** was more stable than **TS1b** with a significant energy advantage of over 6 kcal/mol (see ESI† for more details). The optimized geometry of **TS1a** exhibited a much stronger interaction between OMe and H than **TS1b**. Therefore, the complex **III** prefered **TS1a** route to **TS1b** and palladacycle **IV** was formed. Reductive elimination of **IV** afforded the desired cyclopropane compound **3** and regenerated Pd(0) **I**.

In conclusion, a novel and highly efficient Pd(0)-catalyzed domino cyclopropanation reaction has been established. The process involves a Heck-type coupling and a C(sp^3)–H bond activation. Benzyl bromide is coupled with norbornenes *via* Pd(0)-catalyzed [2+1] cycloaddition reaction and a series of cyclopropane-fused tricyclo-compounds were synthesized. DFT calculations suggest that a four-membered palladacycle transition state is involved. Application of this Pd(0)-catalyzed cycloaddition reaction *via* C(sp^3)–H Bond activation to other biologically significant compounds is currently underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**.]. See DOI: 10.1039/b000000x/.

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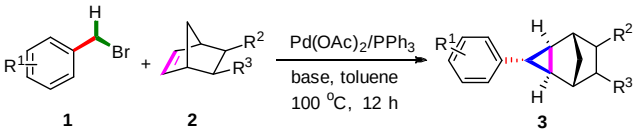

1 **2** **3**

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